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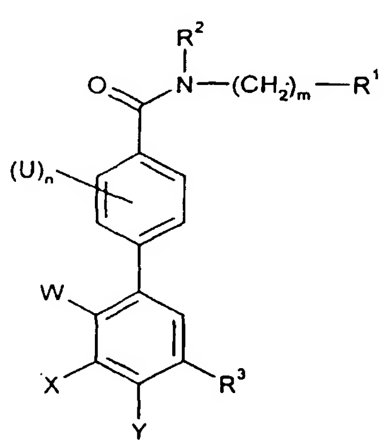
(54) Title: 5'-CARBAMOYL-2'-METHYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KINASE INHIBITORS



(I)

(57) **Abstract:** Compounds of formula (I) or pharmaceutically acceptable salts or solvates thereof, and their use as pharmaceuticals, particularly as p38 kinase inhibitors.

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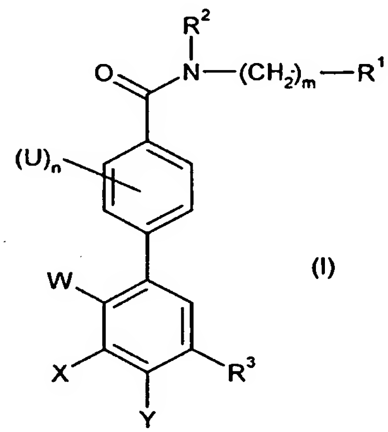
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

5'-CARBAMOYL-2'-METHYL-1,1'-BIPHENYL-4-CARBOXAMIDE DERIVATIVES AND THEIR USE AS P38 KINASE INHIBITORS

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of certain diseases and conditions.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



(I)

wherein

R^1 is a phenyl group which may be optionally substituted;

R^2 is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_v-C_{3-7}$cycloalkyl;

R^3 is the group $-CO-NH-(CH_2)_q-R^4$;

when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6}alkyl, $-C_{3-7}$cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8, heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8;

and when q is 2 R^4 is additionally selected from C_{1-6}alkoxy, $NHCOR^5$, $NHCONHR^5$, NR^5R^6, and OH;

R^5 is selected from hydrogen, C_{1-6}alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6}alkyl and halogen;

R^6 is selected from hydrogen and C_{1-6}alkyl;

or R^5 and R^6, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^7 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-CONR^6R^9$, $-NHCOR^9$, $-SO_2NHR^9$, $-NHSO_2R^9$, halogen, trifluoromethyl, $-Z-(CH_2)_s$-phenyl optionally substituted by one or more halogen atoms, $-Z-(CH_2)_s$-heterocyclyl or $-Z-(CH_2)_s$-heteroaryl wherein the

heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6}alkyl;

R^8 is selected from C_{1-6}alkyl and halogen;

or when R^7 and R^8 are adjacent to each other they may, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6}alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chlorine;

X and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m is selected from 0, 1, 2, 3 and 4, and may be optionally substituted with up to two groups selected independently from C_{1-6}alkyl;

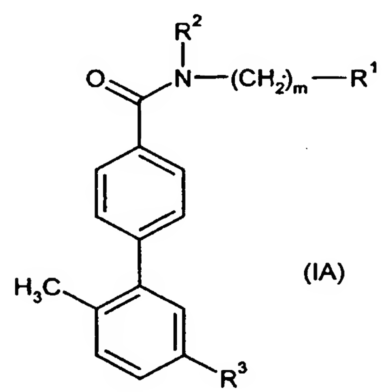
n is selected from 0, 1 and 2;

v is selected from 0, 1 and 2;

q and s are selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

According to a further embodiment of the invention there is provided a compound of formula (IA):



(IA)

wherein R^1, R^2, R^3 and m are as defined above, or a pharmaceutically acceptable salt or solvate thereof.

In a preferred embodiment, the molecular weight of a compound of formula (I) does not exceed 1000, more preferably 800, even more preferably 600.

The group R^1 may be optionally substituted by up to three substituents, more preferably one or two substituents, selected independently from the group consisting of halogen, C_{1-6}alkyl, C_{1-6}alkoxy, trifluoromethyl, benzyloxy, hydroxy, cyano, hydroxyC_{1-6}alkyl, $-(CH_2)_pCO(CH_2)_tNR^{10}R^{11}$, $-(CH_2)_pCO_2R^{10}$, $-(CH_2)_pNR^{10}COR^{11}$, $-(CH_2)_pOCOR^{10}$, -

$(CH_2)_pOCONR^{10}R^{11}$, $-(CH_2)_pNR^{10}COOR^{11}$, $-(CH_2)_pCOR^{10}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^{10}SO_2R^{11}$, $-SO_2R^{10}$, $-(CH_2)_pNR^{10}R^{11}$, $-O(CH_2)_pNR^{10}R^{11}$, $-(CH_2)_pNR^{10}CO(CH_2)_tNR^{10}R^{11}$, $-(CH_2)_pCONR^{10}SO_2R^{11}$, $-(CH_2)_pSO_2NR^{10}COR^{11}$ and phenyloxy optionally substituted by a group A; or R^1 may be optionally substituted by two adjacent substituents which, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system. The ring that is fused to the phenyl ring may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur. The group R^1 may also be optionally substituted by three, more preferably one or two, C_{3-7}cycloalkyl groups.

R^{10} and R^{11} are independently selected from hydrogen, C_{1-6}alkyl, trihalomethyl, benzyl, $-(CH_2)_rOH$, $-(CH_2)_rNR^{12}R^{13}$ and phenyl optionally substituted by up to three groups selected from C_{1-6}alkyl and C_{1-6}alkoxy. R^{10} and R^{11} may also be independently selected from C_{1-6}alkyl substituted by up to three, more preferably one or two, hydroxy groups.

R^{12} and R^{13} are independently selected from hydrogen and C_{1-4}alkyl.

A is selected from halogen, $-SO_2NH_2$, $-SO_2$-(4-methyl)piperazinyl, $-NR^{10}COC_{1-6}$alkyl and $-NR^{10}SO_2C_{1-6}$alkyl.

p is selected from 0, 1, 2 or 3.

t is selected from 0, 1, 2 and 3.

r is selected from 2 or 3.

The optional substituents on the group R^1, including when the phenyl ring is part of a fused bicyclic system, may be located on any position on the phenyl ring. In a more preferred embodiment, when there is one substituent on the group R^1, that substituent is located on the meta- or para-position relative to the amide linkage. When there are two optional substituents on the group R^1, these substituents preferably occupy the meta- and para-positions relative to the amide linkage.

Preferred substituents for the group R^1 are halogen, C_{1-4}alkyl, trifluoromethyl, C_{1-4}alkoxy, phenyloxy optionally substituted by the group A, benzyloxy, hydroxy, cyano, $-CH_2CH_2OH$, $-(CH_2)_p-NHCH_3$, $-(CH_2)_p-N(CH_3)_2$, $-(CH_2)_pCONR^{10}R^{11}$, $-(CH_2)_pCO_2R^{10}$, $-(CH_2)_pNR^{10}COR^{11}$, $-(CH_2)_pOCOR^{10}$, $-(CH_2)_pOCONR^{10}R^{11}$, $-(CH_2)_pNR^{10}COOR^{11}$, $-(CH_2)_pCOR^{10}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^{10}SO_2R^{11}$, $-SO_2R^{10}$, $-(CH_2)_pNR^{10}R^{11}$, $-(CH_2)_pNR^{10}CONR^{10}R^{11}$ and $-(CH_2)_pCONR^{10}SO_2R^{11}$.

Further preferred substituents for the group R^1 include $-CH_2OH$.

More preferred substituents for the group R^1 include halogen, in particular fluorine or chlorine; C_{1-4}alkyl, in particular methyl; C_{1-4}alkoxy, in particular methoxy; hydroxy; cyano; hydroxyC_{1-4}alkyl, in particular $-CH_2OH$ or $-CH_2CH_2OH$; $-(CH_2)_pCO(CH_2)_tNR^{10}R^{11}$, in particular $-CONH_2$ or $-CH_2CONH_2$; $-(CH_2)_pSO_2NR^{10}R^{11}$, in particular $-SO_2NH_2$; $-(CH_2)_pNR^{10}SO_2R^{11}$, in particular $-NHSO_2CH_3$ or $-CH_2NHSO_2CH_3$; $-SO_2R^{10}$, in particular $-SO_2(CH_2)_2OH$; and $-(CH_2)_pNR^{10}R^{11}$, in particular $-CH_2N(CH_3)_2$, $-CH_2N(CH_3)(CH_2CH_3)$ or $-NHCH(CH_2OH)_2$.

In a preferred embodiment, R^2 is selected from hydrogen, C_{1-4}alkyl and $-CH_2$-cyclopropyl, more preferably hydrogen. In further preferred embodiment, R^2 is selected from hydrogen, methyl and ethyl.

In a preferred embodiment, R^4 is selected from C_{1-4}alkyl, cyclopropyl, $-CH_2$-cyclopropyl, pyridinyl and phenyl. In further preferred embodiment, R^4 is selected from C_{1-4}alkyl, in particular ethyl or isopropyl; $-C_{3-7}$cycloalkyl, in particular cyclopropyl, cyclobutyl or cyclopentyl, especially cyclopropyl; phenyl optionally substituted by R^7 and/or R^8, in particular phenyl optionally substituted by C_{1-4}alkyl, C_{1-4}alkoxy, $-CONH_2$, $-CONHCH_3$, $-NHCOCH_3$, $-SO_2NH_2$, $-NHSO_2CH_3$, halogen, and/or $-Z-(CH_2)_s$heteroaryl wherein the heteroaryl is preferably pyridyl, pyrimidyl or oxadiazolyl optionally substituted by C_{1-4}alkyl or phenyl optionally substitued with adjacent groups which give a fused bicyclic ring system, especially quinolinyl, isoquinolinyl or tetralonyl; heteroaryl optionally substituted by R^7 and/or R^8, in particular thienyl, pyridyl or benzofuran optionally substituted by C_{1-4}alkyl and/or $-CONH_2$; and $NHCONHR^5$, in particular where R^5 is phenyl.

In a preferred embodiment, R^5 is selected from hydrogen and C_{1-4}alkyl. In a further preferred embodiment, R^5 is selected from phenyl optionally substituted by C_{1-4}alkyl, in particular methyl.

In a preferred embodiment, R^6 is selected from hydrogen and C_{1-4} alkyl. In particular, R^6 is selected from hydrogen or methyl.

In a preferred embodiment, R^7 is selected from C_{1-4}alkyl, $-NHCOCH_3$, pyridinyl, pyrimidinyl and oxadiazolyl. In a further preferrred embodiment, R^7 is selected from C_{1-4}alkyl, in particular methyl; C_{1-4}alkoxy, in particular methoxy; $-CONR^6R^9$, in particular $-CONHCH_3$ or $CONH_2$; $-NHCOR^9$, in particular $-NHCOCH_3$; $-SO_2NHR^9$, in particular $-SO_2NH_2$; $-NHSO_2R^9$, in particular $-NHSO_2CH_3$; halogen, in particular chlorine; and $-Z-(CH_2)_s$heteroaryl wherein the heteroaryl is preferably pyridyl, pyrimidyl or oxadiazolyl optionally substituted by C_{1-4}alkyl.

In a preferred embodiment, R^8 is selected from C_{1-4} alkyl, fluorine and chlorine. In particular, R^8 is selected from methyl and chlorine.

In a preferred embodiment, R^9 is selected from hydrogen and methyl.

In a preferred embodiment, R^{10} and R^{11} are independently selected from hydrogen, C_{1-4}alkyl, trifluoromethyl and phenyl. In a further preferred embodiment, R^{10} and R^{11} are independently selected from hydrogen; C_{1-4}alkyl, in particular methyl or t-butyl; or C_{1-4}alkyl substituted by up to three, more preferably one or two, hydroxy groups, in particular 2-hydroxyethyl or 1,3-dihydroxyprop-2-yl.

In a preferred embodiment, R^{12} and R^{13} are independently selected from hydrogen, C_{1-4}alkyl and trifluoromethyl.

In a preferred embodiment, W is methyl.

In a preferred embodiment, X and Y are each selected independently from hydrogen, chlorine and fluorine. In a further preferred embodiment, X is fluorine.

In a preferred embodiment, Z is a bond.

In a preferred embodiment, m is selected from 0, 1 and 2.

In a preferred embodiment, n is selected from 0 and 1. In particular, n is 0.

In a preferred embodiment, p is selected from 0, 1 and 2.

In a preferred embodiment, q is selected from 0 and 1. In one embodiment, q is 0.

In a preferred embodiment, s is selected from 0 and 1.

In a preferred embodiment, t is selected from 0, 1 and 2.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts and solvates. Specific examples which may be mentioned include:

$N^{4'}$-(3-Cyanophenyl)-N^3-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-cyclopropyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide; and

N^3-Cyclopropyl-$N^{4'}$-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.

Further specific examples which may be mentioned include:

N^3-Cyclopropyl-5-fluoro-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-{3-[(methylsulfonyl)amino]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-$N^{4'}$-(3-methoxybenzyl)-$N^{4'}$,6-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-$N^{4'}$-[2-(4-methoxyphenyl)ethyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^3-Cyclopropyl-6-methyl-$N^{4'}$-{3-[(methylsulfonyl)amino]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-(3-Bromobenzyl)-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-6-methyl-$N^{4'}$-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-6-methyl-$N^{4'}$-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-[4-(Aminosulfonyl)benzyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-{3-[(dimethylamino)methyl]benzyl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-(3-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-(2-hydroxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-[3-(Aminosulfonyl)phenyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-(2,6-difluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-(2,6-dimethoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

$N^{4'}$-Benzyl-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide;

N^{3}-Cyclopropyl-$N^{4'}$-(4-fluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide; and

N^{3}-Cyclopropyl-$N^{4'}$-(2,6-dimethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C_{1-4}alkyl group is preferred, for example methyl, ethyl or isopropyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms, for example, trifluoromethyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C_{1-4}alkoxy group is preferred, for example methoxy or ethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl,

cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{3-5}cycloalkyl group is preferred, for example cyclopropyl.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic five- to seven- membered unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl. A particularly preferred heteroaryl ring is pyridyl. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy. The terms "heteroaryl ring" and "heteroaryl" also refer to fused aromatic rings comprising at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the fused ring each have five or six ring atoms. Examples of fused aromatic rings include, but are not limited to, indolyl, benzofuranyl and benzothiophenyl, in particular benzofuranyl.

As used herein, the terms "heterocyclic rings" and "heterocyclyl" refer to a monocyclic three- to seven-membered saturated or non-aromatic, unsaturated hydrocarbon ring containing at least one heteroatom selected from oxygen, nitrogen and sulfur. Preferably, the heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, aziridinyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy.

As used herein, the term "fused bicyclic ring system" refers to a ring system comprising two five- to seven-membered saturated or unsaturated hydrocarbon rings, the ring system optionally containing one or more heteroatoms independently selected from oxygen, nitrogen and sulfur. Preferably, each ring has five or six ring atoms. Examples of suitable fused bicyclic rings include, but are not limited to, naphthyl, indolyl, indolinyl, benzothienyl, quinolyl, isoquinolyl, tetrahydroquinolyl, benzodioxanyl, indanyl and tetrahydronaphthyl. Each ring may be optionally substituted with one or more substitutents selected from halogen, C_{1-6}alkyl, oxy, $-(CH_2)_pNR^{10}R^{11}$, $-CO(CH_2)_pNR^{10}R^{11}$, and imidazolyl. Particularly preferred substituents are chlorine, imidazolyl and $-CH_2-N(CH_3)_2$.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s) which occur and events that do not occur.

As used herein, the term "substituted" refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. Most preferably the solvent used is water.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

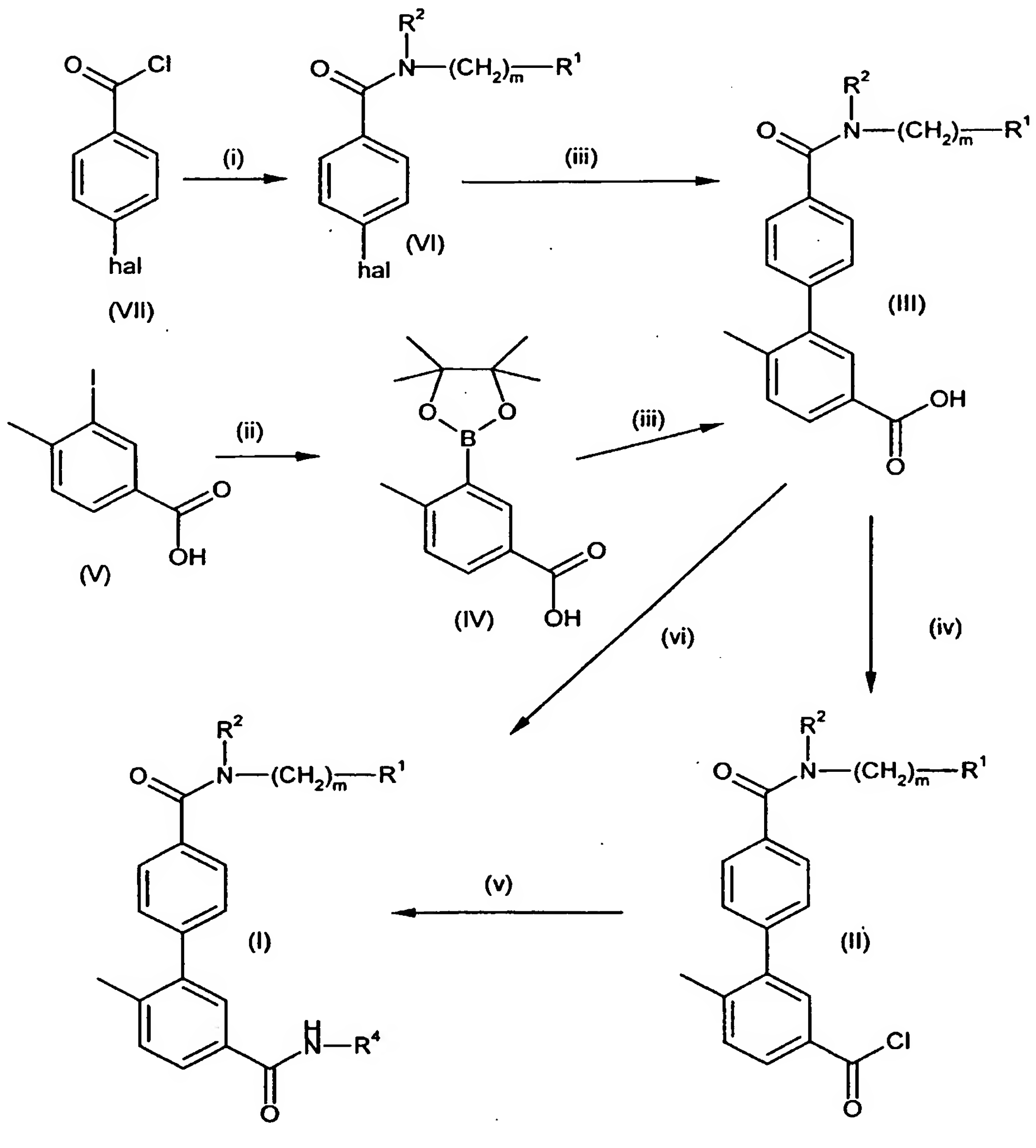
Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulfate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulfate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are

set out below and then specific compounds of the invention are prepared in the working Examples.

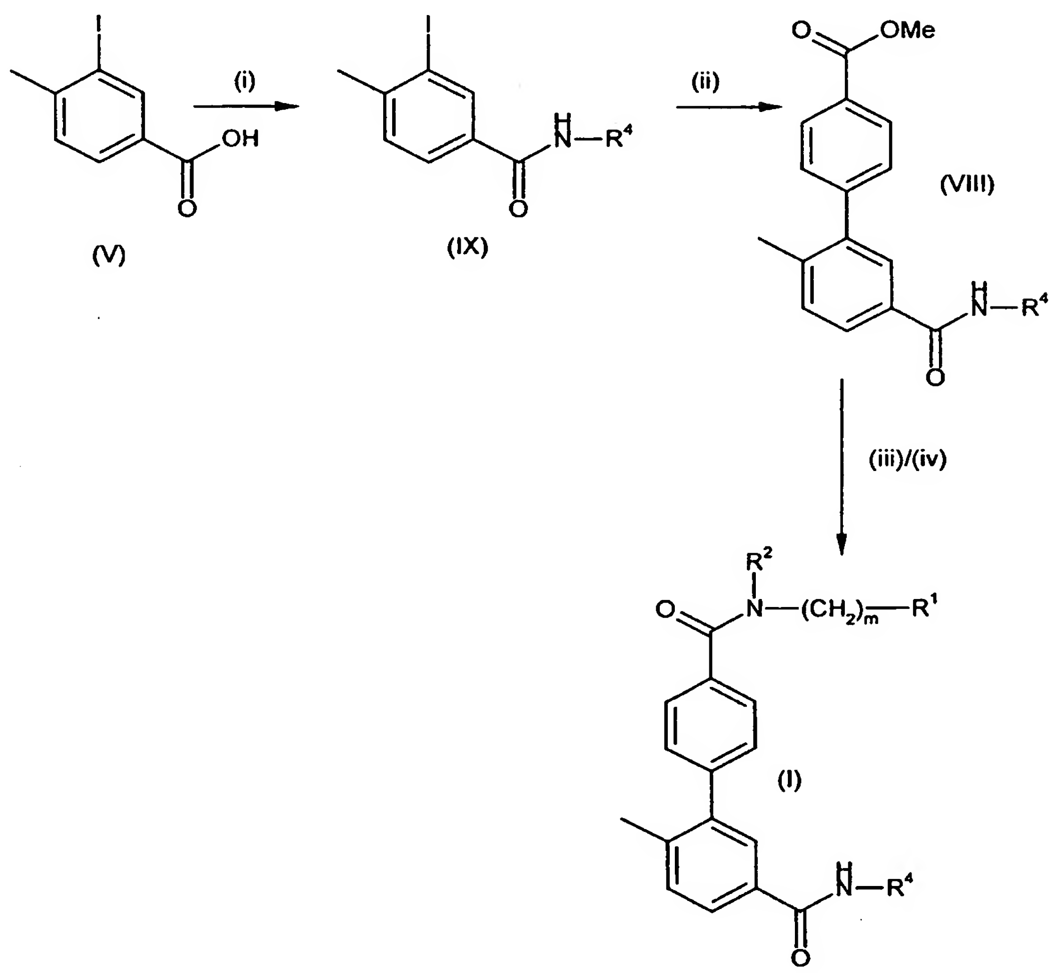
For example, a general method (A) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 1 below.



Scheme 1

(i) $R^1(CH_2)_mN\,R^2H$, Et_3N, THF
(ii) Bis(pinnacolato)diboron, $PdCl_2dppf$, KOAc, DMF
(iii) $(Ph_3P)_4Pd$, Na_2CO_3, DME
(iv) $(COCl)_2$, DMF
(v) R^4NH_2, pyridine
(vi) R^4NH_2, PyBOP, HOBT, DIPEA, DMF

For example, a general method (B) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 2 below.

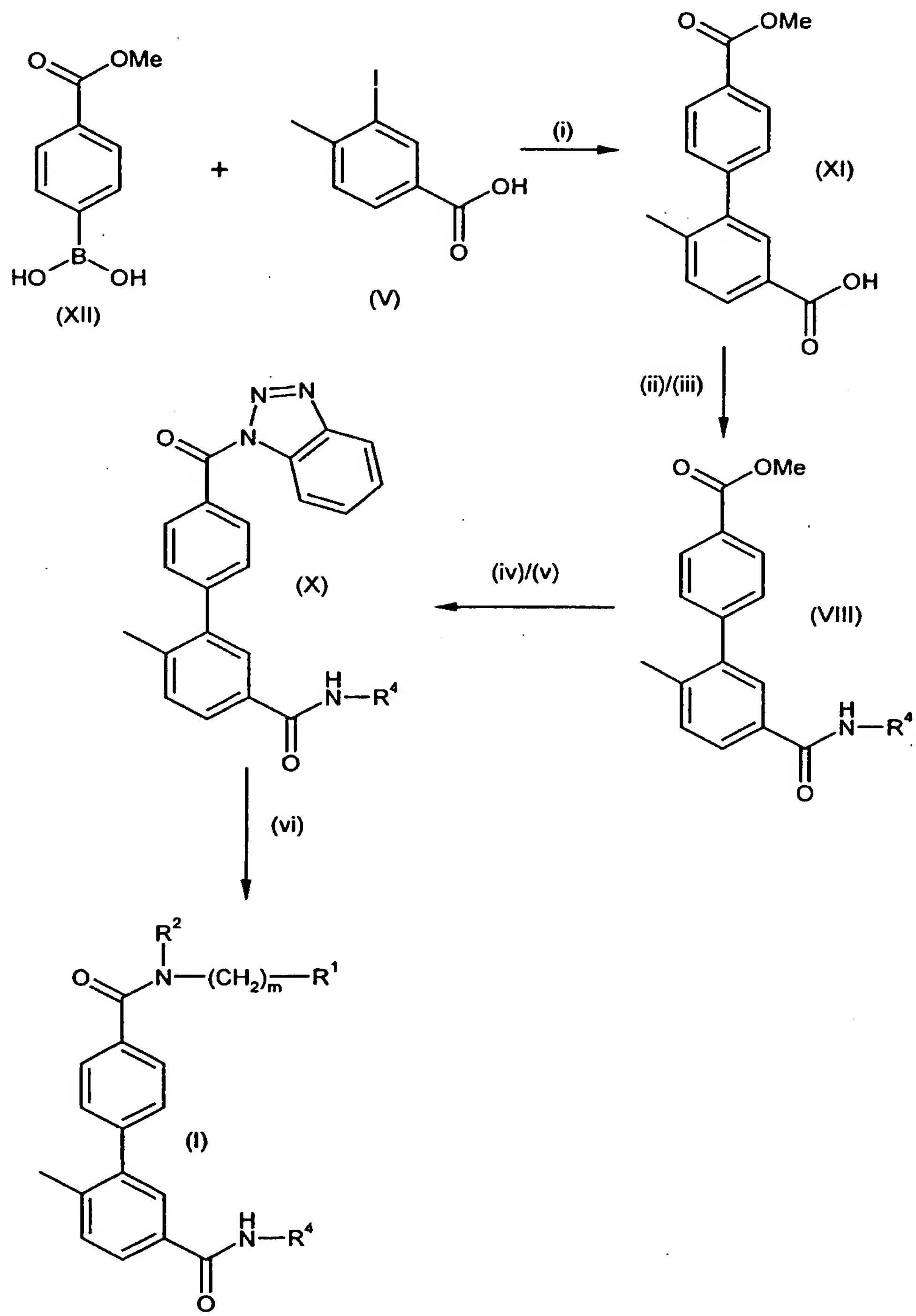


Scheme 2

(i) R^4NH_2, HATU, HOBT, DIPEA, DMF

(ii) (4-Methoxycarbonylphenyl)boronic acid, $(Ph_3P)_4Pd$, Na_2CO_3, DME
(iii) NaOH, MeOH, H_2O
(iv) $R^1(CH_2)_mN\ R^2H$, HATU, HOBT, DIPEA, THF

For example, a general method (C) for preparing the compounds of Formula (I) comprises the reactions set out in Scheme 3 below.

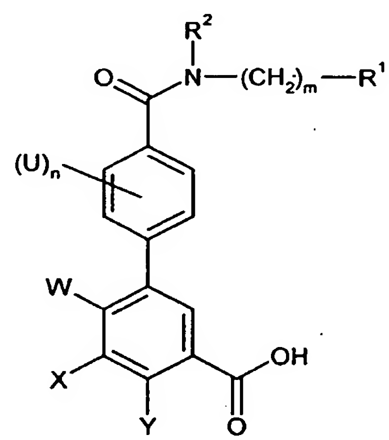

OMe
HO
B
OH
(XII)
+
I
OH
O
(V)
(i)
OMe
(XI)
OH
(ii)/(iii)
OMe
(VIII)
H
N
R4
(iv)/(v)
N
N
N
(X)
(vi)
R2
N
(CH2)m
R1
(I)

Scheme 3

(i) $CsCO_3$, $(Ph_3P)_4Pd$, DME
(ii) $(COCl)_2$, $CHCl_3$
(iii) R^4NH_2
(iv) NaOH, MeOH, H_2O
(v) 1-methylsulphonylbenzotriazole, Et_3N, THF, DMF
(vi) $R^1(CH_2)_mN\ R^2H$, THF

Thus, according to the invention there is provided a process for preparing a compound of formula (I) which comprises:

(a) reacting a compound of formula (XIII)



(XIII)

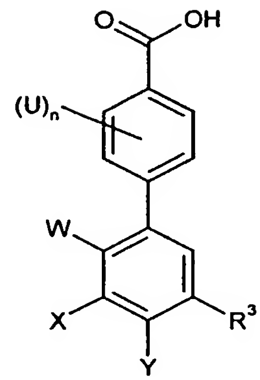
wherein R^1, R^2, U, W, X, Y, m and n are as defined above,
with a compound of formula (XIV)

$$R^4\text{-}(CH_2)_q\text{-}NH_2$$

(XIV)

wherein R^4 and q are as defined above,
under amide forming conditions (if desired, the acid compound (XIII) may be converted to an activated form of the acid, for example the acid chloride, by treatment with, for example, oxalyl chloride, and then the activated acid thus formed reacted with the amine compound (XIV));

(b) reacting a compound of formula (XV)



(XV)

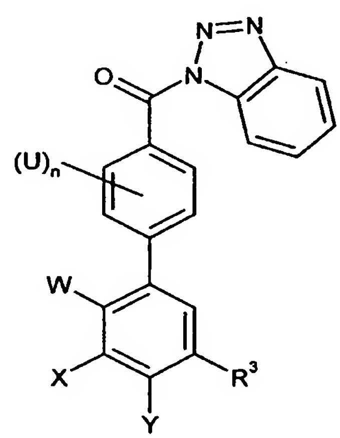
wherein R^3, U, W, X, Y and n are as defined above, with a compound of formula (XVI)

$$R^1(CH_2)_mNR^2H$$

(XVI)

wherein R^1, R^2 and m are as defined above, under amide forming conditions;

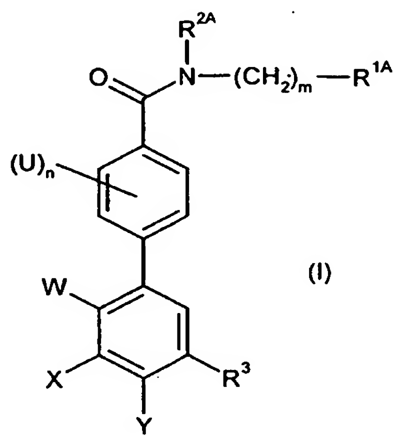
(c) reacting a compound of formula (XVII)



(XVII)

wherein R^3, U, W, X, Y and n are as defined above, with a compound of formula (XVI) as defined above; or

(d) functional group conversion of a compound of formula (XVIII)



(I)

(XVIII)

wherein R^3, U, W, X, Y and n are as defined above and R^{1A} and R^{2A} are R^1 and R^2 as defined above or groups convertible to R^1 and R^2,
to give a compound of formula (I).

Suitable amide forming conditions are well known in the art and include treating a solution of the acid, in for example THF, with an amine in the presence of, for example, HOBT, HBTU and DIPEA.

Whilst it is possible for the compounds, salts or solvates of the present invention to be administered as the new chemical, the compounds of formula (I) and their pharmaceutically acceptable salts and solvates are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compounds of formula (I) and their pharmaceutically acceptable salts and solvates may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable salts and solvates. A particularly preferred method of administration, and corresponding formulation, is oral administration.

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills,

powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be

provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 µg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in

most cases, dose is from about 100 µg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0. 1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) or a salt or solvate thereof, for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It will be appreciated that the compounds of the invention may be selective for one or more of the isoforms of p38, for example p38α, p38β, p38γ and/or p38δ. In one embodiment, the compounds of the invention selectively inhibit the p38α isoform. In another embodiment, the compounds of the invention selectively inhibit the p38β isoform. In a further embodiment, the compounds of the invention selectively inhibit the p38α and p38β isoforms. Assays for determining the selectivity of compounds for the p38 isoforms are described in, for example, WO 99/61426, WO 00/71535 and WO 02/46158.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to

said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis,

and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula(I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain which comprises administering to said subject a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by p38 kinase activity.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, and cancer including breast cancer, colon cancer, lung cancer or prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy, and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of a condition or disease state selected from rheumatoid

arthritis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy.

A further aspect of the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for the preparation of a medicament for the treatment of any type of pain including chronic pain, rapid onset of analgesis, neuromuscular pain, headache, cancer pain, acute and chronic inflammatory pain associated with osteoarthritis and rheumatoid arthritis, post operative inflammatory pain, neuropathic pain, diabetic neuropathy, trigeminal neuralgia, post-hepatic neuralgia, inflammatory neuropathies and migraine pain.

The compounds of formula (I) and their salts, solvates and physiologically functional salts and solvates may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and at least one other pharmaceutically active agent. The compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. The amounts of the compound(s) of formula (I) or pharmaceutically acceptable salt(s) or solvate(s) thereof and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) and their salts and solvates for rheumatoid arthritis therapy include: immunosuppresants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNFα agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychoroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

Examples

The following examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

LCMS was conducted on a column (3.3cm x 4.6mm ID, 3um ABZ+PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm.

General method A:

DIPEA (44µl) was added to a mixture of benzoic acid (0.084mmol), HOBT (0.084mmol), PyBOP (0.084mmol) and amine (0.1mmol) in DMF (0.5ml) and the reaction was stirred at room temperature for 17hours. The DMF was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The organic fraction was chromatographed on a silica SPE (5g) eluting with DCM, chloroform, diethyl ether, ethyl acetate, acetonitrile, acetone, ethanol and methanol or DCM/ethanol/ammonia (1:0:0, 300:8:1, 200:8:1, 100:8:1). The product fractions were combined and evaporated to dryness to give the amide.

General method B:

DIPEA (44µl) was added to a mixture of benzoic acid (0.084mmol), PyBOP (0.084mmol) and amine (0.1mmol) in DCM (2ml) and the reaction was stirred at room temperature for 18hours. The reaction was washed with aqueous sodium carbonate solution (1M, 2ml) and the organic fraction was chromatographed on a silica SPE (5g) eluting with DCM, chloroform, diethyl ether, ethyl acetate, acetonitrile, acetone, ethanol, methanol and DCM/ethanol/ammonia (20:8:1 then 15:8:1). The product fractions were combined and evaporated to dryness to give the amide.

General method C:

Benzoic acid (0.1mmol), HATU (0.1mmol), HOBT (0.1mmol), DIPEA (0.3mmol), and amine (0.1mmol) were mixed in DMF (1ml) and heated for 18hours at 80°C. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was reduced to dryness under vacuum and the amide purified as specified in the example.

General method D:

Benzoic acid (0.17mmol), HATU (0.2mmol), HOBT (0.17mmol), DIPEA (0.51mmol), and amine (0.2mmol) were mixed in DMF (2ml) and the reaction stirred at room temperature for 24hours. Further portions of amine (0.05mmol) and HATU (0.052mmol) were added and the mixture heated for 18hours at 60°C. The solvent was evaporated under vacuum and the residue partitioned between DCM (5ml) and aqueous sodium carbonate (1M, 5ml). The organic phase was reduced to dryness under vacuum and the amide purified as specified in the example.

Example 1: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-(pyrid-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

(a) $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-(pyrid-4-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-aminomethylpyridine using method A. NMR: δH [$^{2}H_{6}$] – DMSO 10.64,(1H, s), 9.16,(1H, t), 8.49,(2H, d), 8.28,(1H, s), 8.09-8.05,(3H, m), 7.85,(1H, dd), 7.82,(1H, d), 7.61-7.58,(4H, m), 7.46,(1H, d), 7.30,(2H, d), 4.49,(2H, d), 2.31,(3H, s). LCMS: retention time 2.96min, MH^{+}447.

(b) (4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid
4-Bromo-N-(3-cyanophenyl)benzamide (2.0g, 6.64mmol), (3-carboxy-6-methylphenyl)pinnacol borane (1.74g, 6.64mmol), tetrakis(triphenylphosphine)palladium (768mg, 0.664mmol) and aqueous sodium carbonate (1M, 60ml) in DME (120ml) were heated at 90°C for 21h. The organic phase was absorbed onto silica and purified by flash chromatography (silica) eluting with DCM/ethanol/ammonia (40:8:1 then 20:8:1) to give (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid (1.06g, 45%). LCMS: retention time 3.53min,[M-H]$^{-}$355.

(c) (3-Carboxy-6-methylphenyl)pinnacol borane
3-Iodo-4-methylbenzoic acid (3.34g, 12.74mmol), bis(pinnacolato)diboron (6.47g, 25.48mmol), potassium acetate (6.27g, 63.7mmol), and 1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride (1.045g, 1.27mmol) in DMF (100ml) were heated at 80°C for 18h. The reaction was concentrated under vacuum and the residue partitioned between ethyl acetate (200ml) and hydrochloric acid (2N, 200ml). The aqueous phase was extracted with ethyl acetate (2 x 150ml). The combined organics were washed with brine (300ml), dried (magnesium sulphate) and absorbed onto silica. Purified by flash chromatography on silica eluting with cyclohexane/ethyl acetate (5:1), the product fractions concentrated under vacuum and triturated with cyclohexane to give (3-carboxy-6-methylphenyl) pinnacol borane (1.81g, 54%). HPLC: retention time 3.54min.

(d) 4-Bromo-N-(3-cyanophenyl)benzamide
3-Aminobenzonitrile (2.7g, 22.8mmol) and triethylamine (3ml) were dissolved in THF (5ml) and 4-bromobenzoylchloride (22.8mmol) added over 5min. The reaction was stirred at room temperature for 1.5h and then partitioned between ethyl acetate and water. The organic phase was washed with brine, the solvent evaporated under vacuum and the residue triturated with cyclohexane to give 4-bromo-N-(3-cyanophenyl)benzamide (5.3g, 77%). LCMS: retention time 3.58min, MH^{+}301/303.

Example 2: N^3-(2-Benzofuran-2-ylethyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-(2-Benzofuran-2-ylethyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 2-(2-aminoethyl)benzofuran using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 8.69,(1H, t), 8.28,(1H, m), 8.09-8.04,(3H, m), 7.77,(1H, dd), 7.72,(1H, d), 7.60-7.55,(4H, m), 7.52,(1H, m), 7.47,(1H, d), 7.42,(1H, d), 7.23-7.15,(2H, m), 6.65,(1H, s), 3.63,(2H, q), 3.04,(2H, t), 2.29,(3H, s). LCMS: retention time 3.78min, MH^+500.

Example 3: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[2-(3-phenylureido)ethyl]-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[2-(3-phenylureido)ethyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 1-(2-aminoethyl)-3-phenylurea using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 8.60,(1H, t), 8.53,(1H, s), 8.29,(1H, s), 8.07-8.05,(3H, m), 7.81,(1H, dd), 7.77,(1H, s), 7.62-7.56,(4H, m), 7.43,(1H, d), 7.36,(2H, d), 7.18,(2H, t), 6.86,(1H, t), 6.25,(1H, t), 3.30,(4H, m), 2.30,(3H, s). LCMS: retention time 3.45min, MH^+518.

Example 4: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(4-sulphamoylbenzyl)-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(4-sulphamoylbenzyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(aminomethyl)benzenesulphonamide using method A. NMR: δH [$^2H_6$] – DMSO 9.16,(1H, t), 8.28,(1H, s), 8.07-8.05,(3H, m), 7.85,(1H, dd), 7.81,(1H, d), 7.76,(2H, d), 7.59-7.57,(4H, m), 7.48-7.44,(3H, m), 4.52,(2H, d), 2.31,(3H, s). LCMS: retention time 3.46min, MH^+525.

Example 5: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(2-{[(4-methylphenyl)amino]carbonyl}ethyl)-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(2-{[(4-methylphenyl)amino]carbonyl}ethyl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]-carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-amino-N-(4-methylphenyl)propanamide using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 9.86,(1H, s), 8.63,(1H, t), 8.28,(1H, s), 8.08-8.05,(3H, m), 7.78,(1H, dd), 7.74,(1H, d), 7.60-7.55,(4H, m), 7.46-7.40,(3H, m), 7.06,(2H, d), 3.53,(2H, q), 2.58,(2H, t), 2.29,(3H, s), 2.22,(3H, s). LCMS: retention time 3.54min, MH^+517.

Example 6: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-{3-[(methylamino)carbonyl]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-{3-[(methylamino)carbonyl]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-(aminomethyl)-N-methylbenzamide using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 9.11,(1H, t), 8.42,(1H, m), 8.28,(1H, m), 8.08-8.05,(3H, m), 7.85,(1H, dd), 7.81,(1H, d), 7.78,(1H, s), 7.68,(1H, d), 7.60-7.58,(4H, m), 7.45,(2H, d), 7.39,(1H, t), 4.51,(2H, d), 2.76,(3H, d), 2.31,(3H, s). LCMS: retention time 3.42min, MH^+503.

Example 7: N^3-(4-Carbamoylbenzyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-(4-Carbamoylbenzyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(aminomethyl)benzamide using method A. NMR: δH [$^2H_6$] – DMSO 10.66,(1H, s), 9.12,(1H, t), 8.28,(1H, m), 8.07-8.05,(3H, m), 7.91,(1H, b), 7.86-7.80,(4H, m), 7.60-7.53,(4H, m), 7.44,(1H, d), 7.36,(2H, d), 7.31,(1H, b), 4.52,(2H, d), 2.31,(3H, s). LCMS: retention time 3.35min, MH^+489.

Example 8: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(methylsulphonamido)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(methylsulphonamido)benzyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and N-[3-(aminomethyl)phenyl]methanesulphonamide using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 9.72,(1H, s), 9.08,(1H, t), 8.28,(1H, m), 8.08-8.05,(3H, m), 7.84,(1H, dd), 7.80,(1H, d), 7.60-7.58,(4H, m), 7.44,(1H, d), 7.27,(1H, t), 7.16,(1H, m), 7.06,(2H, m), 4.44,(2H, d), 2.95,(3H, s), 2.31,(3H, s). LCMS: retention time 3.39min, MH^+539.

Example 9: $N^{4'}$-(3-Cyanophenyl)-N^3-cyclopropylmethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-N^3-cyclopropylmethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and cyclopropylmethylamine using method A. NMR: δH [$^2H_6$] – DMSO 10.63,(1H, s), 8.58,(1H, t), 8.29,(1H, m), 8.09-8.05,(3H, m), 7.81,(1H, dd), 7.76,(1H, d), 7.59-7.57,(4H, m), 7.42,(1H, d), 3.13,(2H, t), 2.30,(3H, s), 1.01,(1H, m), 0.42,(2H, m), 0.21,(2H, m). LCMS: retention time 3.62min, MH^+410.

Example 10: $N^{4'}$-(3-Cyanophenyl)-N^3-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and cyclopropylamine using method A. NMR: δH [$^{2}H_{6}$] – DMSO 10.62,(1H, s), 8.44,(1H, d), 8.28,(1H, m), 8.09-8.05,(3H, m), 7.77,(1H, dd), 7.72,(1H, d), 7.60-7.56,(4H, m), 7.40,(1H, d), 2.84,(1H, m), 2.29,(3H, s), 0.68,(2H, m), 0.55,(2H, m). LCMS: retention time 3.49min, MH^{+}396.

Example 11: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-(quinolin-5-ylmethyl)-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-quinolin-5-ylmethyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 5-aminomethylquinoline using method B. NMR: δH [$^{2}H_{6}$] – DMSO 10.64,(1H, s), 9.13,(1H, t), 8.91,(1H, dd), 8.65,(1H, d), 8.27,(1H, m), 8.07-8.04,(3H, m), 7.94,(1H, d), 7.86,(1H, dd), 7.81,(1H, d), 7.72,(1H, m), 7.59-7.56,(6H, m), 7.44,(1H, d), 4.96,(2H, d), 2.30,(3H, s). LCMS: retention time 3.55min, MH^{+}497.

Example 12: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-tetralon-6-yl -1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^{3}-tetralon-6-yl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 6-aminotetralone using method C and purified by preparative HPLC. LCMS: retention time 3.74min, MH^{+}500.

Example 13: N^{3}-(3-Chlorophenyl) -$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^{3}-(3-Chlorophenyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-chloroaniline using method C and purified by preparative HPLC. NMR: δH [$^{2}H_{6}$] – DMSO 10.64,(1H, s), 10.38,(1H, s), 8.29,(1H, m), 8.10-8.06,(3H, m), 7.96,(1H, t), 7.93,(1H, dd), 7.88,(1H, d), 7.71,(1H, m), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.37,(1H, t), 7.15,(1H, m), 2.34,(3H, s). LCMS: retention time 3.95min, MH^{+}466.

Example 14: N^{3}-(2-Carbamoylthiophen-3-yl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

(a) (4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-aminothiophene-2-carboxamide (19mg, 0.13mmol) in pyridine (1ml) were heated at 70°C for 17h. Water was added to the cooled reaction and the precipitate which formed filtered off and dried to give N^{3}-(2-carbamoylthiophen-3-yl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (24mg, 38%).

NMR: δH [$^2H_6$] – DMSO 12.46,(1H, s), 10.67,(1H, s), 8.29,(1H, m), 8.11-8.05,(4H, m), 7.88,(1H, dd), 7.80,(1H, d), 7.78,(1H, d), 7.62-7.55,(5H, m), 2.34,(3H, s). LCMS: retention time 3.69min, MH^+481.

(b) (4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid (500mg, 1.4mmol), oxalyl chloride (214mg, 1.68mmol) and DMF (2drops) in DCM (20ml) were stirred at room temperature for 2.5h. The solution was concentrated under vacuum to give (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (520mg, 99%). NMR: δH $CDCl_3$ 8.24,(2H, d), 8.04,(1H, dd), 7.98,(1H, d), 7.52,(1H, d), 7.46-7.43,(3H, m), 7.31,(1H, m), 7.25,(1H, m), 2.37,(3H, s).

<u>Example 15: N$^{4'}$-(3-Cyanophenyl)-N^3-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide</u>

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 4-methoxyaniline (21mg, 0.13mmol) in pyridine (1ml) were heated at 70°C for 17h. Water was added to the cooled reaction, the mixture extracted with ethyl acetate and the organic extract reduced to dryness under vacuum. The residue was purified by chromatography on a silica flash column eluting with DCM/ethanol/ammonia (400:8:1), which after concentration of the product fractions under vacuum and trituration with diethyl ether gave N$^{4'}$-(3-cyanophenyl)-N^3-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (10mg, 17%). NMR: δH [$^2H_6$] – DMSO 10.64,(1H, s), 10.12,(1H, s), 8.29,(1H, s), 8.08,(3H, m), 7.91,(1H, d), 7.87,(1H, s), 7.67-7.58,(6H, m), 7.48,(1H, d), 6.92,(2H, d), 3.73,(3H, s), 2.33,(3H, s). LCMS: retention time 3.71min, MH^+462.

<u>Example 16: N^3-(2-Chlorophenyl)-N$^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide</u>

N^3-(2-Chlorophenyl)-N$^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 2-chloroaniline using method C. Purified by preparative HPLC. LCMS: retention time 3.93min, MH^+466.

<u>Example 17: N$^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(3-methylpyrid-4-yl)-1,1'-biphenyl-3,4'-dicarboxamide</u>

N$^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(3-methylpyrid-4-yl)-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-amino-3-methylpyridine using method C. Purified by preparative HPLC. NMR: δH [$^2H_6$] – DMSO 10.67,(1H, s), 9.99,(1H, s), 8.42,(1H, s),

8.37,(1H, d), 8.29,(1H, m), 8.09-8.07,(3H, m), 7.93,(1H, dd), 7.88,(1H, d), 7.63,(2H, d), 7.60-7.57,(3H, m), 7.52,(1H, d), 2.35,(3H, s), 2.26,(3H, s). LCMS: retention time 2.99min, MH^+447.

Example 18: N^3-(3-Acetylaminophenyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-(3-Acetylaminophenyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3'-aminoacetanilide using method C. Purified by preparative HPLC. NMR: δH [$^2H_6$] – DMSO 10.67,(1H, s), 10.25,(1H, s), 9.96,(1H, s), 8.29,(1H, m), 8.09-8.07,(4H, m), 7.92,(1H, dd), 7.88,(1H, d), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.49,(1H, d), 7.41,(1H, d), 7.30,(1H, d), 7.23,(1H, t), 2.34,(3H, s), 2.03,(3H, s). LCMS: retention time 3.51min, MH^+489.

Example 19: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-pyrid-3-yl-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-pyrid-3-yl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 3-aminopyridine using method C. Purified by preparative HPLC. NMR: δH [$^2H_6$] – DMSO 10.65,(1H, s), 10.44,(1H, s), 8.92,(1H, d), 8.31-8.29,(2H, m), 8.20-8.17,(1H, m), 8.10-8.07,(3H, m), 7.95,(1H, dd), 7.91,(1H, d), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.52,(1H, d), 7.40-7.37,(1H, m), 2.34,(3H, s). LCMS: retention time 3.41min, MH^+433.

Example 20: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(2-methylpyrimidin-4-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 4-(3-aminophenyl)-2-methylpyrimidine using method C. Purified by preparative HPLC. NMR: δH [$^2H_6$] – DMSO 10.66,(1H, s), 10.47,(1H, s), 8.76,(1H, d), 8.57,(1H, m), 8.29,(1H, m), 8.10-8.07,(3H, m), 8.05-8.03,(1H, m), 7.97,(1H, dd), 7.95,(1H, d), 7.88,(1H, m), 7.82,(1H, d), 7.65,(2H, d), 7.60-7.58,(2H, m), 7.54-7.50,(2H, m), 2.68,(3H, s), 2.35,(3H, s). LCMS: retention time 3.75min, MH^+524.

Example 21: $N^{4'}$-(3-Cyanophenyl)-N^3-(isoquinolin-5-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

$N^{4'}$-(3-Cyanophenyl)-N^3-(isoquinolin-5-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 5-aminoisoquinoline using method C. Purified by preparative

HPLC. NMR: δH [$^2H_6$] – DMSO 10.66,(1H, s), 10.57,(1H, s), 9.35,(1H, s), 8.52,(1H, d), 8.29,(1H, m), 8.10-8.02,(6H, m), 7.89-7.53,(8H, m), 2.37,(3H, s). LCMS: retention time 3.41min, MH$^+$483.

<u>Example 22: N$^{4'}$-(3-Cyanophenyl)-N^3-(isoquinolin-6-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide</u>

N$^{4'}$-(3-Cyanophenyl)-N^3-(isoquinolin-6-yl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from (4'-{[(3-cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carboxylic acid and 6-aminoisoquinoline using method C. Purified by preparative HPLC. NMR: δH [$^2H_6$] – DMSO 10.66,(1H, s), 10.63,(1H, s), 9.19,(1H, s), 8.53,(1H, d), 8.43,(1H, d), 8.30,(1H, m), 8.11-8.08,(4H, m), 8.00-7.95,(3H, m), 7.76,(1H, d), 7.65,(2H, d), 7.60-7.59,(2H, m), 7.53,(1H, d), 2.36,(3H, s). LCMS: retention time 3.30min, MH$^+$483.

<u>Example 23: N$^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[4-(pyrid-3-ylmethoxy)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide</u>

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-(4-aminophenoxymethyl)pyridine (53mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N$^{4'}$-(3-cyanophenyl)-6-methyl-N^3-[4-(pyrid-3-ylmethoxy)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δH [$^2H_6$] – DMSO 10.67,(1H, s), 10.15,(1H, s), 8.66,(1H, d), 8.54,(1H, dd), 8.29,(1H, m), 8.09-8.06,(3H, m), 7.91,(1H, dd), 7.87-7.85,(2H, m), 7.68,(2H, d), 7.63-7.58,(4H, m), 7.49,(1H, d), 7.43-7.40,(1H, m), 7.02,(2H, d), 5.13,(2H, s), 2.33,(3H, s). LCMS: retention time 3.58min, MH$^+$539.

<u>Example 24: N$^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-(2-methylpyridin-3-yl)-1,1'-biphenyl-3,4'-dicarboxamide</u>

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-amino-2-methylpyridine (29mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N$^{4'}$-(3-cyanophenyl)-6-methyl-N^3-(2-methylpyridin-3-yl)-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δH [$^2H_6$] – DMSO 10.65,(1H, s), 10.08,(1H, s), 8.33,(1H, dd), 8.29,(1H, m), 8.09-8.07,(3H, m), 7.94,(1H, dd), 7.91,(1H, d), 7.73,(1H, dd), 7.63,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.27,(1H, m), 2.43,(3H, s), 2.92,(3H, s). LCMS: retention time 3.21min, MH$^+$447.

Example 25: N^3-[4-(Acetylamino)phenyl]-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 4-(acetylamino)aniline (40mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N^3-[4-(acetylamino)phenyl]-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide. LCMS: retention time 3.50min, MH^+490.

Example 26: N^3-(3-Carbamoyl-4-methylphenyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 5-amino-2-methylbenzamide (40mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give N^3-(3-carbamoyl-4-methylphenyl)-$N^{4'}$-(3-cyanophenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δH [$^2H_6$] – DMSO 10.65,(1H, b), 10.25,(1H, s), 8.29,(1H, s), 8.10-8.07,(3H, m), 7.92,(1H, dd), 7.89,(1H, d), 7.77,(1H, d), 7.74,(1H, dd), 7.69,(1H, b), 7.62,(2H, d), 7.59-7.56,(2H, m), 7.50,(1H, d), 7.36,(1H, b), 7.18,(1H, d), 2.34,(3H, s), 2.31,(3H, s). LCMS: retention time 3.38min, MH^+489.

Example 27: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 2-(3-aminophenyl)pyridine (45mg, 0.26mmol) in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give $N^{4'}$-(3-cyanophenyl)-6-methyl-N^3-[3-(pyrid-2-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. NMR: δH [$^2H_6$] – DMSO 10.67,(1H, s), 10.39,(1H, s), 8.67,(1H, d), 8.51,(1H, t), 8.30,(1H, m), 8.10-8.07,(3H, m), 7.98-7.87,(5H, m), 7.79,(1H, d), 7.65,(2H, d), 7.60-7.58,(2H, m), 7.51,(1H, d), 7.47,(1H, t), 7.36,(1H, m), 2.35,(3H, s). LCMS: retention time 3.81min, MH^+509.

Example 28: $N^{4'}$-(3-Cyanophenyl)-6-methyl-N^3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide

(4'-{[(3-Cyanophenyl)amino]carbonyl}-6-methyl-1,1'-biphenyl-3-yl)carbonyl chloride (50mg, 0.13mmol) and 3-(3-aminophenyl)-5-methyl-1,2,4-oxadiazole (47mg, 0.26mmol)

in pyridine (1ml) were heated at 70°C for 15h. The pyridine was evaporated from the reaction under vacuum and the residue partitioned between ethyl acetate and water. The organic fraction was concentrated under vacuum and purified by preparative HPLC to give $N^{4'}$-(3-cyanophenyl)-6-methyl-N^3-[3-(5-methyl-1,2,4-oxadiazol-3-yl)phenyl]-1,1'-biphenyl-3,4'-dicarboxamide. LCMS: retention time 3.80min, MH^+514.

Example 29: N^3-Cyclopropyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-Cyclopropyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 3-methoxybenzylamine using method D. Purified by chromatography on silica, eluting with a toluene/methanol (9:1). NMR: δH [$^2H_6$] – DMSO 9.11,(1H, t), 8.44,(1H, d), 7.99,(2H, d), 7.76,(1H, dd), 7.70,(1H, d), 7.49,(2H, d), 7.40,(1H, d), 7.26,(1H, m), 6.91,(2H, m), 6.83,(1H, m), 4.49,(2H, d), 3.74,(3H, s), 2.85,(1H, m), 2.28,(3H, s), 0.69,(2H, m), 0.55,(2H, m). LCMS: retention time 3.22min, MH^+ 415.

Example 30: N^3-Cyclopropyl-$N^{4'}$-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

N^3-Cyclopropyl-$N^{4'}$-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide was synthesised from 3'-[(cyclopropylamino]carbonyl]-6'-methyl-1,1'-biphenyl-4-yl)carboxylic acid and 4-methoxyaniline using method D. Purified by chromatography on silica, eluting with a toluene/methanol (19:1). NMR: δH [$^2H_6$] – DMSO 10.19,(1H, s), 8.44,(1H, d), 8.03,(2H, d), 7.76,(1H, dd), 7.69,(3H, m), 7.52,(2H, d), 7.40,(1H, d), 6.93,(2H, d), 3.74,(3H, s), 2.84,(1H, m), 2.28,(3H, s), 0.68,(2H, m), 0.58,(2H, m). LCMS: retention time 3.26min, MH^+ 401.

Example 31: N^3-Cyclopropyl-5-fluoro-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 32: N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-{3-[(methylsulfonyl)amino]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide

Example 33: N^3-Cyclopropyl-5-fluoro-6-methyl-$N^{4'}$-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide

General Method E:

{3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1, 31mg, 0.10mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21mg, 0.11mmol), HOBT (15mg, 0.11mmol) and the appropriate amine (0.11mmol) were dissolved in DMF (4ml). DIPEA (19µl, 0.11mmol) was added to the

solution which was then stirred for 5 hours at 40°C. Ethyl acetate (25ml) and water (25ml) were added. The ethyl acetate layer was separated and washed sequentially with aqueous sodiumhydrogen carbonate and hydrochloric acid (0.5M). The solvent was removed *in vacuo* and the residue was purified by mass-directed HPLC.

Compound	Amine	MH^+	Retention time (minutes)
Example 31	3-methoxybenzylamine	433	3.26
Example 32	N-(3-aminomethylphenyl)methane-sulphonamide	496	3.02
Example 33	N-(4-aminophenyl)methane-sulphonamide	482	3.19

(a) {3'-[(Cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 1)

3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2,120mg, 0.45mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (111mg, 0.45mmol) and tetrakis(triphenylphosphine) palladium (51mg, 0.045mmol) were dissolved in DME (3ml) and aqueous sodium carbonate (1M, 450µl) was added. The mixture was refluxed at 80°C for 16 hours. Solvent was removed *in vacuo* and the residue was purified by silica biotage chromatography, eluting with 2:1 ethyl acetate:cyclohexane followed by 9:1 ethyl acetate:methanol. To give {3'-[(cyclopropylamino)carbonyl]-5'-fluoro-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (129mg, 91%).
LCMS: MH^+ 314, retention time 3.06 min.

(b) 3-Bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (Intermediate 2)

3-Fluoro-4-methylbenzoic acid (462mg, 3.0mmol) was added to a stirred mixture of bromine (2.31ml, 45mmol) and iron powder (252mg, 4.5mmol) under nitrogen. The reaction was stirred at 20°C for 4 hours and then left to stand for 16 hours. Sodium thiosulphate solution (200ml) was added and the product was extracted into ethyl acetate (3 x 150ml). Ethyl acetate extracts were combined and evaporated *in vacuo*. The crude product (mixture of isomers) was dissolved in DMF(7ml). Cyclopropylamine (208µl, 3.0mmol), HOBT (405mg, 3.0mmol), 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide hydrochloride (575mg, 3.0mmol) and DIPEA (525µl, 3.0mmol) were added to the stirred solution. The reaction was stirred for 5 hours at 20°C. Solvent was removed *in vacuo* and the residue was partitioned between ethyl acetate and water. Combined ethyl acetate extracts were washed sequentially with aqueous sodium hydrogen carbonate and hydrochloric acid (0.5M), then dried (magnesium sulphate). The ethyl acetate was evaporated *in vacuo* and the residue was purified by silica biotage chromatography eluting with cyclohexane:ethyl acetate (6:1)to give 3-bromo-N-cyclopropyl-5-fluoro-4-methylbenzamide (359mg, 44%).
NMR: δH – $CDCl_3$ 7.68,(1H, s), 7.39,(1H, d), 6.19,(1H, bs), 2.88,(1H, m), 2.36,(3H, d), 0.88,(2H, m), 0.63,(2H, m). LCMS: MH^+ 272/274, retention time 3.12 min.

Example 34: N^3-Cyclopropyl-$N^{4'}$-(3-methoxybenzyl)-$N^{4'}$,6-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 35: N^3-Cyclopropyl-$N^{4'}$-(4-methoxyphenyl)-$N^{4'}$,6-dimethyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 36: N^3-Cyclopropyl-$N^{4'}$-[2-(4-methoxyphenyl)ethyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 37: N^3-Cyclopropyl-6-methyl-$N^{4'}$-{3-[(methylsulfonyl)amino]benzyl}-1,1'-biphenyl-3,4'-dicarboxamide

Example 38: N^3-Cyclopropyl-$N^{4'}$-{3-[(dimethylamino)methyl]-1H-indol-5-yl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

General Method F:

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), the chosen amine (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at 80°C under nitrogen for 16 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, methanol and DCM:ethanol:ammonia (20:8:1) to give the desired products.

Compound	Amine	MH^+	Retention time (minutes)
Example 34	N-(3-methoxybenzyl)-N-methylamine	429	3.26

Example 35	N-(4-methoxyphenyl)-N-methylamine	415	3.06
Example 36	2-(4-methoxyphenyl)ethylamine	429	3.24
Example 37	N-(3-aminomethylphenyl) methanesulphonamide	478	2.88
Example 38	5-amino-3-(dimethylaminomethyl)-indole	467	2.38

Example 39: $N^{4'}$-(3-Bromobenzyl)-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

HATU (1.29g, 3.39mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (1g, 3.39mmol) in THF (20ml). After 5 minutes HOBT (0.46g, 3.39mmol), 3-bromobenzylamine hydrochloride (0.905g, 4.07mmol) and DIPEA (2.5, 14.24mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The THF was removed *in vacuo*. The residue was partitioned between ethyl acetate (50ml) and water (50ml). The aqueous layer was extracted with ethyl acetate (50ml) and the organic extracts were washed with aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate) and the solvent removed *in vacuo* to yield $N^{4'}$-(3-bromobenzyl)-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (1.56g, 3.37mmol).

NMR: δH [$^{2}H_6$] – DMSO 9.18,(1H, bt), 8.43,(1H, bd), 7.99,(2H,d), 7.77,(1H, dd), 7.70,(1H, d), 7.54,(1H, t), 7.50,(2H, d), 7.46,(1H, dt), 7.39,(1H, d), 7.36,(1H, dt), 7.32,(1H, t), 4.50,(2H, d), 2.85,(1H, m), 2.28,(3H, s), 0.72-0.53,(4H, 2xm). LC/MS: MH^+ 463/465, retention time 3.36minutes

Example 40: N^{3}-Cyclopropyl-6-methyl-$N^{4'}$-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), N-(4-aminophenyl)methanesulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The reaction was partitioned between ethyl acetate (50ml) and hydrochloric acid (1M, 50ml). The organic layer was washed with aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate), and the solvent removed *in vacuo*. The crude material was purified by SPE cartridge (Si, 5g) eluting in turn with DCM:ethanol:ammonia (400:8:1), ethyl acetate, acetonitrile, acetone and ethanol to yield the N^{3}-cyclopropyl-6-methyl-$N^{4'}$-{4-[(methylsulfonyl)amino]phenyl}-1,1'-biphenyl-3,4'-dicarboxamide.

LC/MS: MH^+ 464, retention time 2.96minutes

Example 41: N^3-Cyclopropyl-6-methyl-$N^{4'}$-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), N-(4-aminobenzyl)methanesulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The reaction was partitioned between ethyl acetate (50ml) and hydrochloric acid (1M, 50ml). The organic layer was washed with aqueous sodium carbonate (1M, 50ml), brine (25ml), dried (magnesium sulphate), and the solvent removed *in vacuo.* The crude material was purified by SPE cartridge (Si, 5g) eluting in turn with DCM:ethanol:ammonia (400:8:1), ethyl acetate, acetonitrile, acetone and ethanol to yield the N^3-cyclopropyl-6-methyl-$N^{4'}$-(4-{[(methylsulfonyl)amino]methyl}phenyl)-1,1'-biphenyl-3,4'-dicarboxamide.
LC/MS: MH^+ 478, retention time 3.03minutes.

Example 42: $N^{4'}$-[4-(Aminosulfonyl)benzyl]-N^3-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), 4-(aminomethyl)phenylsulphonamide (0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, DCM:ethanol:ammonia (40:8:1) DCM:ethanol:ammonia (20:8:1) and DCM:ethanol:ammonia (10:8:1) to give $N^{4'}$-[4-(aminosulfonyl)benzyl]-N^3-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.
LC/MS: MH^+ 464, retention time 2.77minutes.

Example 43: N^3-Cyclopropyl-$N^{4'}$-{3-[(dimethylamino)methyl]benzyl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

HATU (65mg, 0.17mmol) was added to a solution of 3'-[(cyclopropylamino)carbonyl]-6'-methyl-biphenyl-4-carboxylic acid (50mg, 0.17mmol) in DMF (2ml). After 5 minutes HOBT (23mg, 0.17mmol), 3-(dimethylaminomethyl)benzylamine (Intermediate 3, 0.17mmol) and DIPEA (0.087ml, 0.51mmol) were added and the reaction mixture stirred

at room temperature under nitrogen for 18 hours. The DMF was removed *in vacuo* and the residue partitioned between DCM (5ml) and aqueous sodium carbonate solution (1M, 5ml). The layers were separated and the organic layer purified by SPE cartridge (Si, 5g) eluting in turn with DCM, chloroform, ether, ethyl acetate, acetonitrile, acetone, ethanol, DCM:ethanol:ammonia (40:8:1) DCM:ethanol:ammonia (20:8:1) and DCM:ethanol:ammonia (10:8:1) to give N^3-cyclopropyl-$N^{4'}$-{3-[(dimethylamino)methyl]benzyl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide.
LC/MS: MH^+ 442, retention time 2.32minutes.

(a) 3-(Dimethylaminomethyl)benzylamine (Intermediate 3)

A suspension of (3-dimethylaminomethyl-benzyl)carbamic acid *tert*-butyl ester (Intermediate 4, 0.256g, 1mmol) in hydrogen chloride in dioxane (4N, 4ml) was stirred at room temperature under nitrogen for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in water (6ml). This was washed with ethyl acetate (3x 15ml). The aqueous layer was basified by addition of aqueous sodium hydroxide (2N) and extracted with ethyl acetate (2x20ml). The combined organic extracts were dried (magnesium sulphate) and the solvent removed *in vacuo* to give 3-(dimethylaminomethyl)benzylamine (0.060g, 0.37mmol).
MS: MH^+ 165.

(b) (3-Dimethylaminomethylbenzyl)carbamic acid *tert*-butyl ester (Intermediate 4)

A solution of (3-chloromethylbenzyl)carbamic acid *tert* butyl ester (Intermediate 5, 1.55g, 6.06mmol) in THF (15ml) was treated with dimethylamine in THF (2M, 12ml, 24mmol). The mixture was heated under reflux under nitrogen for 6 hours. The solvent was removed *in vacuo* and the residue partitioned between chloroform (50ml) and aqueous sodium hydrogen carbonate (50ml). The organic layer was dried (magnesium sulphate), and the solvent removed *in vacuo* to give the desired product (1.37g, 5.18mmol).
MS: MH^+ 265.

(c) (3-Chloromethylbenzyl)carbamic acid *tert*-butyl ester (Intermediate 5)

Triethylamine (21.27ml, 152.6mmol) was added to a suspension of 3-chloromethylbenzylamine hydrochloride (Intermediate 6, 167.92mmol) in dry THF (180ml). A solution of di-tert-butyl dicarbonate (14.75g, 67.58mmol) in dry THF (50ml) was added dropwise at 0°C. Once the addition was complete, the reaction mixture was stirred at room temperature for 18 hours. The mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ethyl acetate (250ml) and washed

with water (150ml). The aqueous layer was extracted with ethyl acetate (50ml). The combined organic extracts were washed with cold hydrochloric acid (1N, 80ml), aqueous sodiumhydrogen carbonate solution (100ml), dried (magnesium sulphate), filtered and concentrated *in vacuo* to give (3-Chloromethylbenzyl)carbamic acid *tert*-butyl ester (12g, 46.9mmol).
MS: MNH_4^+ 273.

(d) 3-Chloromethylbenzylamine hydrochloride (Intermediate 6)

Hexamethylenetriamine (27.13g, 0.194mol) was added to a solution of dichloro-m-xylene (34g, 0.194mol) in chloroform (230ml) and the mixture heated at reflux for 30minutes. The cooled reaction was filtered and the filtrate reduced to dryness under vacuum. The residue was dissolved in ethanol (340ml), treated with concentrated hydrochloric acid (32ml) and heated at reflux for 3hours. The reaction was reduced to 4ml under vacuum, diluted with ether (250ml) and filtered to give 3-chloromethylbenzylamine hydrochloride (10.57g).
MS: MH^+ 156.

Example 44: N^3-Cyclopropyl-$N^{4'}$-(3-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Four drops of 1-methyl-2-pyrrolidinone were added to anhydrous potassium carbonate (45mg, 0.326mmol), copper (I) iodide (5mg, 0.026mmol), $N^{4'}$-(3-bromobenzyl)-N^3-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (0.1g, 0.216mmol) and serinol (0.5g, 5.49mmol). The reaction mixture was heated at 200°C in a microwave for 15 minutes. The crude reaction mixture was partitioned between ethyl acetate (10ml) and water (10ml). The aqueous layer was extracted with ethyl acetate (2x10ml). The combined organic extracts were washed with water (2x30ml), brine (30ml), dried (magnesium sulphate) and absorbed onto silica gel. Purification was by SPE cartridge (Si, 5g) eluting with a n ehtyl acetate / cyclohexane gradient (0-100% ethyl acetate) to give N^3-cyclopropyl-$N^{4'}$-(3-{[2-hydroxy-1-(hydroxymethyl)ethyl]amino}benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide (5mg, 0.011mmol).
NMR: δH [$^2H_6$] – DMSO 9.02,(1H, bt), 8.43,(1H, bd), 8.00,(2H, d) 7.76,(1H, dd), 7.70,(1H, d), 7.48,(2H, d), 7.39,(1H, d), 7.02,(1H, t), 6.59,(1H, bt), 6.48,(2H, bd), 5.25,(1H, d), 4.59,(2H, t), 4.39,(2H, d), 3.53-3.43,(5H, m), 2.83,(1H, m), 2.28,(3H, s), 0.70-0.52,(4H, 2xm). LC/MS: MH^+ 474, retention time 2.68minutes.

Example 45: N^3-Cyclopropyl-$N^{4'}$-(2-hydroxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 46: $N^{4'}$-[3-(Aminosulfonyl)phenyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 47: N^{3}-Cyclopropyl-$N^{4'}$-(2,6-difluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 48: N^{3}-Cyclopropyl-$N^{4'}$-(2,6-dimethoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 49: $N^{4'}$-Benzyl-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 50: N^{3}-Cyclopropyl-$N^{4'}$-(4-fluorobenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 51: N^{3}-Cyclopropyl-$N^{4'}$-(2,6-dimethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 52: N^{3}-Cyclopropyl-$N^{4'}$-(4-{[ethyl(methyl)amino]methyl}benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 53: N^{3}-Cyclopropyl-$N^{4'}$-[2-(2-hydroxyethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 54: $N^{4'}$-[3-(Aminocarbonyl)benzyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 55: N^{3}-Cyclopropyl-$N^{4'}$-{4-[(dimethylamino)methyl]benzyl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 56: $N^{4'}$-(2-Chlorobenzyl)-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 57: N^{3}-Cyclopropyl-$N^{4'}$-{3-[(2-hydroxyethyl)sulfonyl]phenyl}-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 58: tert-Butyl 3-[({5'-[(cyclopropylamino)carbonyl]-2'-methyl-1,1'-biphenyl-4-yl}carbonyl)amino]benzylcarbamate

Example 59: N^{3}-Cyclopropyl-$N^{4'}$-[2-(hydroxymethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 60: N^{3}-Cyclopropyl-$N^{4'}$-(3-{[ethyl(methyl)amino]methyl}benzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 61: N^{3}-Cyclopropyl-$N^{4'}$-(3-hydroxymethylphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 62: $N^{4'}$-[3-(2-Amino-2-oxoethyl)phenyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 63: $N^{4'}$-Benzyl-N^{3}-cyclopropyl-$N^{4'}$-ethyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 64: $N^{4'}$-[2-(Aminocarbonyl)benzyl]-N^{3}-cyclopropyl-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 65: N^{3}-Cyclopropyl-$N^{4'}$-[3-(2-hydroxyethyl)phenyl]-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 66: N^{3}-Cyclopropyl-6-methyl-$N^{4'}$-[(1R)-1-phenylethyl]-1,1'-biphenyl-3,4'-dicarboxamide

General Method G

A solution of {3'-[(cyclopropylamino)carbonyl]-2-methyl-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (50mg, 0.17mmol) in DMF (1ml) was treated with HATU (65mg, 0.17mmol) at room temperature. After 5minutes this was added to a solution of the amine (0.17mmol) and HOBT (23mg, 0.17mmol) in DMF (1ml). DIPEA (87ul, 3eq) was added. The reaction mixture was left at room temperature for 16hrs, then concentrated *in vacuo*.
The residue was dissolved in DCM (1ml) and loaded onto a SPE cartridge (1g, aminopropyl) which had been pre-equilibrated with DCM.
Residual sample was washed on with another portion of DCM (0.5ml) , The cartridge was then eluted with: DCM (1x2.5ml), chloroform (1x2.5ml), ethyl acetate (1x2.5ml), and methanol (1x2.5ml). The fractions containing product were isolated by evaporation to give the desired product.

Compound	Amine	MH^+	Retention time (minutes)
Example 45	2-hydroxybenzylamine	401	3.22
Example 46	3-aminophenyl-sulphonamide	450	2.95
Example 47	2,6-difluorobenzylamine	421	3.26
Example 48	2,6-dimethoxybenzyl-amine	445	3.29
Example 49	benzylamine	385	3.24
Example 50	4-fluorobenzylamine	403	3.28
Example 51	2,6-dimethylbenzylamine	399	3.32
Example 52	4-(N-ethyl-N-	456	2.44

	methylaminomethyl)-benzylamine		
Example 53	2-(2-hydroxyethyl))aniline	415	3.04
Example 54	3-(aminomethyl)-benzamide	428	2.74
Example 55	4-(dimethylaminomethyl)-benzamide	442	2.41
Example 56	2-chlorobenzylamine	419	3.40
Example 57	2-[(3-aminophenyl)-sulphonyl]ethanol	479	3.10
Example 58	3-*tert*-butoxycarbonyl-aminomethylamiline	500	3.47
Example 59	2-(hydroxymethyl)aniline	401	3.46
Example 60	3-(N-ethyl-N-methyl-aminomethyl)benzylamine	456	2.46
Example 61	3-(hydroxymethyl)aniline	401	2.94
Example 62	3-aminophenylacetamide	428	2.80
Example 63	N-benzyl-N-ethylamine	413	3.39
Example 64	2-(aminomethyl)-benzamide	428	2.86
Example 65	3-(2-hydroxyethyl)aniline	415	2.98
Example 66	α-methylbenzylamine	399	3.31

Example 67: N^3-Cyclobutyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 68: N^3-Ethyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 69: N^3-Ethyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 70: N^3-Ethyl-$N^{4'}$-(4-methoxyphenyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 71: N^3-Isopropyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

Example 72: N^3-Cyclopentyl-$N^{4'}$-(3-methoxybenzyl)-6-methyl-1,1'-biphenyl-3,4'-dicarboxamide

General Method H:

The acid (0.06mmol), triethylamine (13ul) and 1-(methylsulphonyl)-1H-benzotriazole (12mg, 0.06mmol) were mixed in THF (0.5ml) and heated at reflux for 4 hours. The reaction was concentrated under vacuum and partitioned between chloroform (3ml) and water (2ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (0.5ml) and was mixed with the amine (0.06mmol). After 20 hours the reaction was loaded onto an SPE (aminopropyl, 0.5g) and eluted with chloroform to give the desired product.

Compound	Acid	Amine	MH^+	Retention time (minutes)
Example 67	{3'-[(Cyclobutylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzyl-amine	429	3.42
Example 68	{3'-[(Cyclobutylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	4-methoxyaniline	415	3.47
Example 69	{3'-[(Ethylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzy-lamine	403	3.24
Example 70	{3'-[(Ethylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	4-methoxyaniline	389	3.29
Example 71	{3'-[(Isopropylamino)-carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	3-methoxybenzyl-amine	417	3.34
Example 72	{3'-[(Cyclopentylamino)-	3-methoxybenzyl-	443	3.50

	carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid	amine		

(a) {3'-[(Cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 7)

Methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 8, 123mg, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (121mg).
LC/MS: MH^+ 310, retention time 3.25minutes.

(b) Methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 8)

4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (217mg, 0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was mixed with cyclobutylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(cyclobutylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (123mg).
LC/MS: MH^+ 324, retention time 3.40minutes.

(c) {3'-[(Ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 9)

Methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 10, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .
LC/MS: MH^+ 284, retention time 2.99minutes.

(d) Methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 10)

4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was mixed with ethylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(ethylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH^+ 298, retention time 3.20minutes.

(e) {3'-[(Isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 11)

Methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 12, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .
LC/MS: MH^+ 298, retention time 3.11minutes.

(f) Methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 12)

4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was mixed with isopropylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(isopropylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH^+ 312, retention time 3.31minutes.

(g) {3'-[(Cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid (Intermediate 13)

Methyl {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 14, 0.38mmol) in methanol (2ml) was mixed with aqueous sodium hydroxide (2N, 1ml) and stirred at room temperature for 24hours. The methanol was evaporated, the reaction diluted with water (2ml) and extracted with chloroform (3ml). The aqueous was acidified with hydrochloric acid (2N, 3ml) and extracted with chloroform (2x 4ml). The solvent was evaporated from the organic extracts to give {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylic acid .
LC/MS: MH^+ 324, retention time 3.37minutes.

(h) Methyl {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate (Intermediate 14)

4'-(Methoxycarbonyl)-2-methyl-1,1'-biphenyl-5-carboxylic acid (0.80mmol), triethylamine (157ul) and 1-(methylsulphonyl)-1H-benzotriazole (158mg, 0.80mmol) were mixed in THF (3.6ml) and heated at reflux for 18 hours. The reaction was concentrated under vacuum and partitioned between chloroform (9ml) and water (6ml) and the organics reduced to dryness under vacuum. The residue was redissolved in THF (2ml) and was mixed with cyclopentylamine (0.1ml). After 3 hours the reaction was loaded onto an SPE (aminopropyl, 10g) and eluted with chloroform to give methyl {3'-[(cyclopentylamino)carbonyl]-6'-methyl-1,1'-biphen-4-yl}carboxylate.
LC/MS: MH^+ 338, retention time 3.52minutes.

<u>Abbreviations</u>

DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBT	1-Hydroxybenzotriazole hydrate
PyBOP	Benzotriazol-1-yl-oxy-tripyrrolidinophosphonium hexafluorophosphate
SPE	Solid phase extraction

THF Tetrahydrofuran

The activity of the compounds of the invention as p38 inhibitors may be demonstrated in the following assays:

p38 Kinase Assay

The peptide substrate used in the p38 assay was biotin-IPTSPITTTYFFFRRR-amide. The p38 and MEK6 proteins were purified to homogeneity from E.coli expression systems. The fusion proteins were tagged at the N-terminus with Glutathione-S-Transferase (GST). The maximum activation was achieved by incubating 20uL of a reaction mixture of 30nM MEK6 protein and 120nM p38 protein in the presence of 1.5uM peptide and 10mM $Mg(CH_3CO_2)_2$ in 100mM HEPES, pH 7.5, added to 15uL of a mixture of 1.5uM ATP with 0.08uCi [g-^{33}P]ATP, with or without 15uL of inhibitor in 6%DMSO. The controls were reactions in the presence (negative controls) or absence (positive controls) of 50 mM EDTA. Reactions were allowed to proceed for 60 min at room temperature and quenched with addition of 50uL of 250mM EDTA and mixed with 150uL of Streptavidin SPA beads (Amersham) to 0.5mg/reaction. The Dynatech Microfluor white U-bottom plates were sealed and the beads were allowed to settle overnight. The plates were counted in a Packard TopCount for 60 seconds. IC_{50} values were obtained by fitting raw data to %I = 100*(1-(I-C2)/(C1-C2)), where I was CPM of background, C1 was positive control, and C2 was negative control.

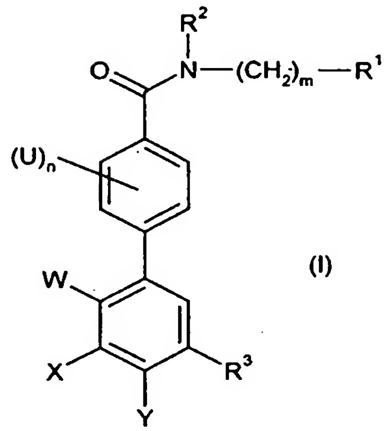
α P38 Fluorescence Polarisation Method

αP38 was prepared in house. SB4777790-R Ligand was diluted in HEPES containing $MgCl_2$, CHAPS, DTT and DMSO. This was added to blank wells of a Black NUNC 384 well plate. αP38 was added to this ligand mixture then added to the remainder of the 384 well plate containing controls and compounds. The plates were read on an LJL Analyst and Fluorescence Anisotropy used to calculate the compound inhibition

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims:

Claims:

1. A compound of formula (I):



(I)

wherein

R^1 is a phenyl group which may be optionally substituted;

R^2 is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_v$-C_{3-7}cycloalkyl;

R^3 is the group $-CO-NH-(CH_2)_q-R^4$;

when q is 0 to 2 R^4 is selected from hydrogen, C_{1-6}alkyl, -C_{3-7}cycloalkyl, $CONHR^5$, phenyl optionally substituted by R^7 and/or R^8, heteroaryl optionally substituted by R^7 and/or R^8 and heterocyclyl optionally substituted by R^7 and/or R^8;

and when q is 2 R^4 is additionally selected from C_{1-6}alkoxy, $NHCOR^5$, $NHCONHR^5$, NR^5R^6, and OH;

R^5 is selected from hydrogen, C_{1-6}alkyl and phenyl wherein the phenyl group may be optionally substituted by up to two substituents selected from C_{1-6}alkyl and halogen;

R^6 is selected from hydrogen and C_{1-6}alkyl;

or R^5 and R^6, together with the nitrogen atom to which they are bound, form a five- to six-membered heterocyclic or heteroaryl ring optionally containing one additional heteroatom selected from oxygen, sulfur and nitrogen, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^7 is selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-CONR^6R^9$, $-NHCOR^9$, $-SO_2NHR^9$, $-NHSO_2R^9$, halogen, trifluoromethyl, $-Z-(CH_2)_s$-phenyl optionally substituted by one or more halogen atoms, $-Z-(CH_2)_s$-heterocyclyl or $-Z-(CH_2)_s$-heteroaryl wherein the heterocyclyl or heteroaryl group may be optionally substituted by one or more substituents selected from C_{1-6}alkyl;

R^8 is selected from C_{1-6}alkyl and halogen;

or when R^7 and R^8 are adjacent to each other they may, together with the carbon atoms to which they are bound, form a five- or six-membered saturated or unsaturated ring to give a fused bicyclic ring system, wherein the ring that is formed by R^7 and R^8 may optionally contain one or two heteroatoms selected from oxygen, nitrogen and sulfur;

R^9 is selected from hydrogen and C_{1-6}alkyl;

U is selected from methyl and halogen;

W is selected from methyl and chloro;

X and Y are each selected independently from hydrogen, methyl and halogen;

Z is selected from -O- and a bond;

m is selected from 0, 1, 2, 3 and 4, and may be optionally substituted with up to two groups selected independently from C_{1-6}alkyl;

n is selected from 0, 1 and 2;

v is selected from 0, 1 and 2;

q and s are selected from 0, 1 and 2;

or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 wherein R^1 is substituted by one or two substituents selected from halogen, C_{1-4}alkyl, trifluoromethyl, C_{1-4}alkoxy, benzyloxy, hydroxy, cyano, $-CH_2CH_2OH$, $-(CH_2)_p-NHCH_3$, $-(CH_2)_p-N(CH_3)_2$, $-(CH_2)_pCONR^5R^6$, $-(CH_2)_pCO_2R^5$, $-(CH_2)_pNR^5COR^6$, $-(CH_2)_pOCOR^5$, $-(CH_2)_pOCONR^5R^6$, $-(CH_2)_pNR^5COOR^6$, $-(CH_2)_pCOR^5$, $-(CH_2)_pSO_2NR^5R^6$, $-(CH_2)_pNR^5SO_2R^6$, $-SO_2R^5$, $-(CH_2)_pNR^5R^6$, $-(CH_2)_pNR^5CONR^5R^6$ and $-(CH_2)_pCONR^5SO_2R^6$;

wherein p is selected from 0, 1 and 2; and

R^5 and R^6 are independently selected from hydrogen, C_{1-4}alkyl and phenyl.

3. A compound according to claim 1 wherein R^1 is substituted by one or two substitutents selected from halogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, cyano, hydroxyC_{1-4}alkyl, $-(CH_2)_pCO(CH_2)_tNR^{10}R^{11}$, $-(CH_2)_pNR^{10}COOR^{11}$, $-(CH_2)_pSO_2NR^{10}R^{11}$, $-(CH_2)_pNR^{10}SO_2R^{11}$, $-SO_2R^{10}$, and $-(CH_2)_pNR^{10}R^{11}$.

4. A compound according to any one of the preceding claims wherein R^2 is selected from hydrogen, C_{1-4}alkyl and $-CH_2$-cyclopropyl.

5. A compound according to claim 4 wherein R^2 is hydrogen.

6. A compound according to any one of the preceding claims wherein m is selected from 0, 1 and 2.

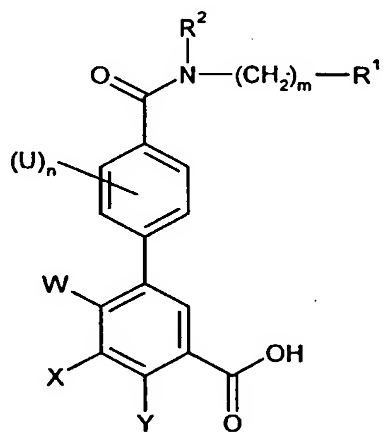
7. A compound according to any one of the preceding claims wherein R^4 is selected from C_{1-4}alkyl, -C_{3-7}cycloalkyl, CONHR^5, phenyl optionally substituted by R^7 and/or R^8, and heteroaryl optionally substituted by R^7 and/or R^8.

8. A compound according to claim 7 wherein R^4 is selected from C_{1-4}alkyl, cyclopropyl, pyridinyl and phenyl.

9. A compound according to claim 1 as defined in any one of Examples 1 to 72, or a pharmaceutically acceptable salt or solvate thereof.

10 A process for preparing a compound according to any one of claims 1 to 9 which comprises:

(a) reacting a compound of formula (XIII)



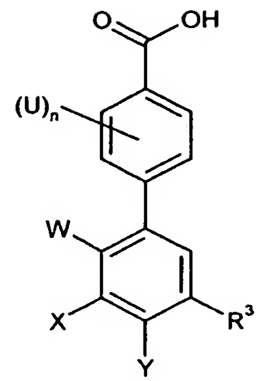
(XIII)

wherein R^1, R^2, U, W, X, Y, m and n are as defined in claim 1, with a compound of formula (XIV)

$$R^4\text{-}(CH_2)_q\text{-}NH_2 \quad \text{(XIV)}$$

wherein R^4 and q are as defined in claim 1, under amide forming conditions, optionally converting the acid compound (XIII) to an activated form of the acid before reaction with the amine compound (XIV);

(b) reacting a compound of formula (XV)



(XV)

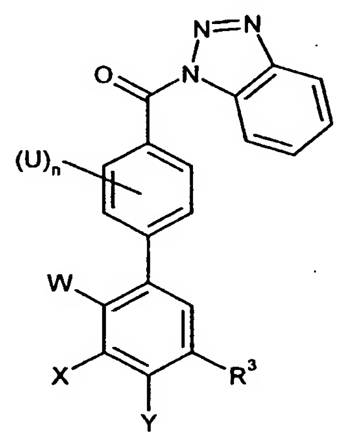
wherein R^3, U, W, X, Y and n are as defined in claim 1, with a compound of formula (XVI)

$$R^1(CH_2)_mNR^2H$$

(XVI)

wherein R^1, R^2 and m are as defined in claim 1, under amide forming conditions;

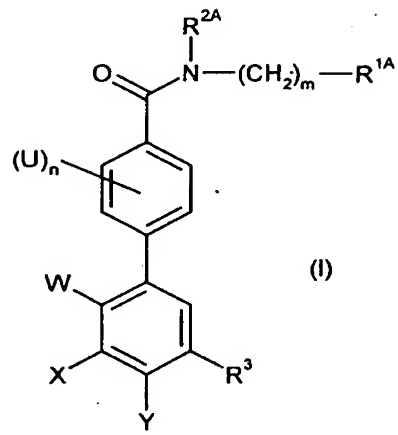
(c) reacting a compound of formula (XVII)



(XVII)

wherein R^3, U, W, X, Y and n are as defined in claim 1, with a compound of formula (XVI) as defined above; or

(d) functional group conversion of a compound of formula (XVIII)



(XVIII)

wherein R^3, U, W, X, Y and n are as defined in claim 1 and R^{1A} and R^{2A} are R^1 and R^2 as defined in claim 1 or groups convertible to R^1 and R^2, to give a compound of formula (I).

11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof, in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

12. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof.

13. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof for use in therapy.

14. Use of a compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 02/11570

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/166 A61K31/167 C07C233/65 C07C233/66 C07C233/73
C07C233/75 C07C233/78 C07C237/22 C07C255/60 C07C271/20
C07C275/28 C07C311/08 C07C311/40 C07C311/46 C07C317/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 849 256 A (JAPAN TOBACCO INC) 24 June 1998 (1998-06-24) page 124 -page 125; claim 1 page 137; claim 16	1-8, 10-14
A	WO 00 41698 A (RIEDL BERND ;LOWINGER TIMOTHY B (JP); DUMAS JACQUES (US); RENICK J) 20 July 2000 (2000-07-20) the whole document	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2003	21/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fink, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11570

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D209/14 C07D213/30 C07D213/40 C07D213/75 C07D215/12 C07D217/02 C07D239/26 C07D271/06 C07D307/81 C07D333/38 C07C237/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

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* Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

Inter   onal Application No
PCT/EP 02/11570

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